REMARKS

Claims 80-106 are currently pending and under consideration in this application. New claims 107-142 have been added in the above amendments. Hence, claims 80-142 will be pending and under consideration upon entry of this amendment.

New independent claims 107 and 128 are directed to sustained release dosage forms comprising oxymorphone and "a plurality of pharmaceutically acceptable substrates." The recited substrates contain a "sustained release matrix material" comprising either: a hydrophilic and/or hydrophobic polymer, digestible long chain hydrocarbon, polyalkylene glycol, or a mixture of the foregoing. For support, the Examiner's attention is invited to the application as filed, *e.g.*, at page 10, line 1-11; and page 26, line 11 to page 28, line 20. New independent claim 128 is directed to an oxymorphone formulation that also contains a "plurality of pharmaceutically acceptable substrates" having a "sustained release matrix material" comprising the same components that are listed in new claim 107. However, claim 128 additionally specifies that the substrates also contain a binder, and a diluent. *See* in the application as originally filed, *e.g.*, at page 28, lines 21-25. New independent claim 132 is directed to dosage forms whose sustained release matrix material comprises either: gum, cellulose ether, acrylic resin, protein-derived material, or a mixture of the foregoing. Support can be found in the application as filed, *e.g.*, at page 26, lines 15-20 as well as in the passages cited *supra*. New independent claim 136 is directed to a process for making sustained release formulations, and recites steps of (a) forming granules of oxymorphone (or a salt thereof) and at least one water soluble hydroxyalkyl cellulose, and (b) mixing the granules with at least one C_{12}-C_{36} aliphatic alcohol. Such methods are described in the application as originally filed, *e.g.*, at page 29, lines 1-12. New claims 108-127, 129-131, 133-135 and 137-142 depend either directly or indirectly from new independent claims 107, 128, 132, and 136, respectively. Support for these dependent claims can therefore be found in the passages cited *supra*. Therefore, none of the newly added claims introduces new matter to this application. The entry and consideration of these new claims are therefore respectfully requested.

I. The Double Patenting Rejection Should Be Withdrawn

Claims 80-106 have been rejected under the judicially created doctrine of obviousness-type double patenting, as being unpatentable over claims 1-17, 19-26 and 28-66 in U.S. Patent No. 5,965,161 ("the '161 patent"). In particular, the '161 patent is said to teach "a sustained-release oral dosage form in the form of a tablet or capsule comprising an opioid analgesic, i.e., oxymorphone, alkylcellulose, a binder, and diluent." The Office Action at page 3, lines 1-3, citing to the '161 patent at column 1, lines 1-10; and at column 4, lines 18-23. The Office Action also notes that dependent claim 83 and 95 in this application specifically claim dosage forms that comprise ethylcellulose, which is said to be an obvious species of hydroxyalkylcellulose described in the '161 patent. In response, Applicants respectfully submit that the rejection for obviousness-type double patenting is improper and should be withdrawn. As explained below, the invention *claimed* in the instant application is non-obvious and patentably distinct from that *claimed* in the '161 patent, and *vice versa*.

"In determining whether a nonstatutory basis exists for a double patenting rejection, the first question to be asked is – does any *claim* in the application define an invention that is merely an obvious variation of an invention *claimed* in the patent?" M.P.E.P. § 804(II)(B)(1) (Rev. 3, August 2005) (emphasis added). "When considering whether the invention defined in a claim of an application would have been an obvious variation of the invention defined in the claim of a patent, the disclosure of the patent may not be used as prior art." *Id.*, citing *General Foods Corp. v. Studiengesellschaft Kohle mbH*, 972 F.2d 1272, 1279, 23 USPQ2d 1839, 1846 (Fed. Cir. 1992). The rejection for double patenting is therefore improper, since it discusses only the '161 patent *specification* without ever even mentioning what is *claimed* by that patent. For this reason alone the double patenting rejection should be withdrawn.

Moreover, the claimed invention of the instant application is non-obvious, and therefore patentably distinct, over anything disclosed or claimed in the '161 patent. In particular, independent claim 80 in this application specifically recites sustained-release dosage forms of oxymorphone that contain a *hydrophilic* polymer. Independent claims 89, 98, 107, and 128 also

specifically recite sustained release formulations that contain a *hydrophilic* polymer. The term "sustained release" release is defined in the application, and specifically refers to:

> the release of the drug (*e.g.*, opioid analgesic [such as oxymorphone]) at such a rate that blood (*e.g.*, plasma) levels are maintained within the therapeutic range but below toxic levels over a period of time *greater than* 12 hours, more preferably for about 24 hours or longer.

See in the application as filed at page 11, line 24 to page 12, line 4 (emphasis added).

In contrast, the '161 patent merely describes and claims a "sustained-release oral dosage form" that contains "an opioid analgesic dispersed in a matrix comprising one or more retardants." *See*, for example, '161 patent claim 1. Although the '161 patent may describe and/or claim certain formulations containing a hydroxyalkylcellulose, it specifically teaches that "[i]f unit doses of the multiparticulate are to have about a 12 hour *or shorter* release pattern, hydroxyalkycelluloses, for example, will be extruded with the therapeutic agent." Hence, any '161 patent formulations using hydroxyalkycellulose or another water soluble polymer as their retardant are not "sustained release formulations," as that term is defined and used in the present application. In particular, such formulations release their active ingredient over a period of time that is *less than*, not *greater than*, 12 hours.

Nor does the '161 patent's alleged use of alkycelluloses (for example, ethylcellulose) render the presently claimed invention obvious. This is because alkycelluloses, as defined in the '161 patent, are a subgenus of *hydrophobic* polymers, not a *hydrophilic* polymer as recited in the instant application's claims. *See* for example in the '161 patent at column 4, lines 32-34 ("The retardant can be a hydrophobic material such as ... alkylcellulose"), and at column 5, lines 41-43 ("In other preferred embodiments, the hydrophobic polymer which may be used is a hydrophobic cellulosic material such as ethylcelllose."). *See also* in the instant application as filed, at page 19, line 24 to page 20, line 2 ("the hydrophobic polymer which may be used for coating the substrates of the present invention is a hydrophobic cellulosic material such as ethylcellulose."). Dependent claims 83 and 95 of this application actually specify that the claimed dosage forms "further compris[e] ethylcellulose." Hence, although certain embodiments of the claimed

compositions may contain an alkycelulose (such as ethylcellulose), it is present *in addition to*, not in place of, the hydrophilic polymer component recited in the independent claims.

For all of the foregoing reasons, Applicants respectfully submit that the rejection for obviousness-type double patenting should be withdrawn.

II. The Rejection for Obviousness Under 35 U.S.C. § 103(a) Should Be Withdrawn

Claims 80-106 have also been rejected under 35 U.S.C. § 103(a) as being unpatentable over the teachings of U.S. Patent No. 5,472,712 by Oshlack *et al.* ("Oshlack" or "the '712 patent") when considered in view of U.S. Patent No. 4,464,378 by Hussain ("Hussain" or "the '378 patent"). This rejection should be withdrawn for the reasons explained below.

At the outset, Applicants respectfully point out that this application claims priority, through a series of continuing applications, as a continuation-in-part of the '712 patent cited in the Office Action. However, the Office Action states that "[t]here is no sufficient support for oxymorphone in [the '712 patent]," and concludes that the instant application is only entitled to an effective filing date of October 7, 1993. The '712 patent, however, issued from an application filed on June 23, 1993. Hence, even if the Examiner's conclusion is correct, the '712 patent can only be available as prior art, if at all, under 35 § 102(e).

Although the '712 patent allegedly does not disclose oxymorphone, it is said to describe controlled-release formulations containing opioid analgesic, as well as methods of treatment using such formulations. The Hussain '378 patent is said to teach "a controlled drug formulation wherein hydromorphone and oxymorphone are taught as equivalent species." *See* in the Office Action at page 5, lines 5-6 (citing to the '378 patent at column 3, lines 10-14). However, contrary to what is stated in the Office Action, the Hussain '378 patent does not teach or even suggest sustained- or controlled-release formulations. Nor does Hussain teach or suggest that oxymorphone and hydromorphone may be equivalents.

Hussain is, in fact, directed to dosage forms for the *nasal* administration of very different narcotic analgesics: morphine, Δ^9-tetrahydrocannabinol, and their analogues. *See* in the Hussain '378 patent at column 2, lines 45-62. These nasal formulations described in Hussain are not sustained- or controlled-release formulations. To the contrary, Hussain's bioavailability data for his formulations show plasma levels of the narcotic analgesic tested (naloxone) are drastically reduced to almost nothing within 180 minutes (*i.e.*, only three hours) after administration. *See*, in Tables I and II at columns 7-8 of Hussain. Sustained release formulations of oxymorphone or any other therapeutic agent are not described, or even mentioned in Hussain's '378 patent.

The passage cited in the Office Action (*i.e.*, column 3, lines 10-14 in Hussain's '378 patent) is merely a Markush group listing what are said to be "[p]articularly significant morphine analogues contemplated by the ['378 patent's] present invention." Although hydromorphone and oxymorphone may be listed in the Hussain patent's Markush group, this passage does not teach or even suggest that they are equivalents. At best, the cited passage only suggests that hydromorphone and oxymorphone may be used particular formulations for *nasal* administration of a narctocie analgesic, as described by Hussain. There is nothing in Hussain to suggest that these analgesics can be substituted as equivalents in other formulations – let alone in sustained release formulations. Nor does Hussain contain any teaching that may give a skilled artisan any reasonable expectation of success. Indeed, since Hussain describes formulations so disparate from those of the presently claimed invention (*i.e.*, nasal as opposed to oral, sustained release dosage forms), the skilled artisan would most likely believe such a substitution would *not* succeed. There is no teaching or suggestion, neither in Hussain nor in the '712 patent, that analgesics which might be interchangeable in certain *nasal* formulations (*e.g.*, those listed in the Hussain '378 patent's cited Markush group) might also be interchangeable in a sustained-release dosage form.

Obviousness can only be established by combining or modifying the prior art to produce the claimed invention where there is some teaching, suggestion or motivation to do so, found either in the references themselves or in the knowledge generally available to one of

ordinary skill in the art. M.P.E.P. § 2143.01. *See* also, *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). The mere fact that references may be combined or modified does not render the resulting combination obvious, unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 143 (Fed. Cir. 1990). The motivation and the reasonable expectation of success must be found in the prior art and not in Applicants' disclosure. *See* M.P.E.P. § 2143 (8th Ed. Rev. 2, May 2004), citing *In re Vaeck*, 947 F.2d 488, USPQ2d 1438 (Fed. Cir. 1991). The references cited in the Office Action, however, fail to provide *either* the requisite motivation to combine or a reasonable expectation of success. In particular, neither the '171 nor the '378 patent suggests that analgesics which might be used interchangeably in a *nasal* formulation can or should be substituted in an oral, sustained-release formulation. Nor do the references provide any reasonable expectation that the analgesics could be successfully interchanged.

For all of the foregoing reasons, Applicants respectfully submit that the rejection under 35 U.S.C. § 103(a) is improper and should be withdrawn.

III. Conclusion

Applicants respectfully submit that the foregoing remarks overcome and/or obviate each basis for rejection set forth in the Office Action. The pending claims (including the new claims presented *supra*) are all believed to be in immediate condition for allowance.

Accordingly, the withdrawal of all objections and rejections is respectfully requested. An allowance is earnestly sought.

Respectfully submitted,

Dated: July 20, 2006

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